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Neuropsychiatry of 18q– Syndrome

Richard N. Mahr, Paul J. Moberg, Joan Overhauser, Gordon Strathdee, John Kamholz, Laurie A. Loevner, Heather Campbell, Elaine H. Zackai, Mark E. Reber, David P. Mozley, Lawrence Brown, Bruce I. Turetsky, and Raymond M. Shapiro

Departments of Psychiatry, Brain-Behavior Laboratory (R.N.M., P.J.M., H.C., M.E.R., B.I.T., R.M.S.), Genetics (E.H.Z.), Neurology (J.K., L.B.), and Radiology (L.A.L., D.P.M.), University of Pennsylvania School of Medicine, and Department of Biochemistry and Molecular Biology (G.S., J.O.), Thomas Jefferson University, Philadelphia, Pennsylvania

Our understanding of neuropsychiatric abnormalities in patients with deletions of the long arm of chromosome 18 (18q– syndrome) is based mainly on sporadic case reports. We characterized the neuropsychiatric phenotype in 27 patients across a wide age range (2–47 years) with breakpoints ranging from 18q22.3–18q21.2. Adaptive behavior scores (Vineland Composite) were significantly higher in females than in males (62 ± 5 vs. 43 ± 3). Intelligence ranged from borderline to severely deficient (IQ, 73–<40), with academic achievement similarly impaired. Performance in specific neuropsychological functions, including attention, novel problem solving, memory, language, visuomotor integration, and fine motor dexterity, was consistently in the moderately-to-severely impaired range. Behavioral problems were common in both sexes, including aggressivity, hyperactivity, and temper tantrums. Contrary to the few previous reports, we found no evidence of psychosis in any patient. In a subset of patients selected on the basis of no prior knowledge of behavioral problems, 1 of 16 patients (6%) had autism, as defined by the Autistic Diagnostic Interview–Revised (ADI-R) [Lord et al., 1994: J Autism Dev Disord 24:659–685]. Thus, the prevalence of autism in 18q– syndrome is probably no greater than that in other developmental disabilities with a similar level of cognitive impairment. In contrast to what has been believed since 18q– was first described 30 years ago, we found no relationship between chromosome deletion size and any measure of cognition or behavior; nor were there any correlations between any of these measures with the presence or absence of abnormalities on MRI or somatosensory-evoked potentials. © 1996 Wiley-Liss, Inc.

KEY WORDS: chromosome 18, intermittent explosive disorder, neuropsychology, mental retardation, partial haploinsufficiency

INTRODUCTION

Patients with terminal deletions of the long arm of chromosome 18 (18q– syndrome) were first described 30 years ago by de Grouchy et al. [1964]. Since then, over 100 cases have been reported, and 18q– is now considered one of the more common autosomal deletion syndromes [Schinzel, 1984]. Dysmorphisms and anomalies associated with 18q– vary, but may include mental retardation, short stature, midface hypoplasia, carp-shaped mouth, oculomotor abnormalities, hearing defects, urogenital malformation, skeletal anomalies, and selective IgA deficiency. For a more complete discussion, see Schinzel [1984] or Miller et al. [1990].

Neuropsychiatric phenotype in 18q– syndrome is not well-known and is based mainly on sporadic case reports. The range of behavioral problems that have been reported includes aggressive outbursts [Bourgeois et al., 1974; Lejeune, 1977; Wilson et al., 1979; Krag-Olsen et al., 1981], autism [Seshadri et al., 1992], "obsessive-compulsive behaviors" [Donnai, 1987], and psychosis [Lejeune, 1977; Donnai, 1987]. Intelligence has been reported to range from low-normal to severely impaired, and language has been hypothesized to be preferentially affected [Schinzel, 1984].

Over the past 30 years, the severity of neuropsychiatric disability in 18q– syndrome has been assumed to be related to chromosomal deletion size. Only recently have molecular techniques become available to directly examine this hypothesis. Kline et al. [1993] used molecular methods to determine breakpoints in 7 patients

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Address reprint requests to Raymond M. Shapiro, M.D., Ph.D., Medical Director, East Ridge Health Systems, 235 South Water St., Martinsburg, WV 25401.

with terminal 18q deletions and concluded that "in general, the size of the deletion could be correlated with the severity of the phenotype." However, their sample size was small, the age range of the patients was limited, and neuropsychiatric phenotype was not assessed systematically.

The present report describes our attempt to define more systematically the range of neuropsychiatric abnormalities associated with terminal 18q deletions, and to determine the extent to which any of these abnormalities may be associated with chromosomal deletion size. Our results argue against any simple relationship between deletion size and any of our measures of central nervous system (CNS) integrity, i.e., adaptive behavior, maladaptive behavior, neuropsychological performance, magnetic resonance imaging (MRI), or somatosensory-evoked potentials.

SUBJECTS AND METHODS

Subjects

Subjects ranged in age from 2–47 years (mean age, 15.9 ± 10.7 years) and were enrolled in this study from as many sources as possible (Table I). Of the 27 patients, 5 were identified by the Clinical Genetics Center at the Children's Hospital of Philadelphia; 7 were referred by pediatricians from various locations throughout the U.S. (5 of these patients were also described by Kline et al. [1993]). Two patients were contacted via authors of journal articles in which the patients were described [Donnai, 1987; Miller et al., 1990]. Four patients were accrued via parent self-referral. In 3 of these 4 cases, behavioral concerns led the parents to seek out additional professional consultation, while in the fourth case it was concern over speech delay (Table I). The other 9 patients were identified through contacts with members of the Parent Support Network of the Chromosome 18 Registry and Research Society. Of the 27 patients in this study, behavioral histories were available in 11 cases. In the other 16 patients, there was no known behavioral history prior to this study. All patients were, or had been, in special education settings.

Assessments

Adaptive behavior. The formal definition of mental retardation requires both a deficit in global adaptive behavior and a deficit in intellectual functioning [DSM-IV, American Psychiatric Association, 1994]. For the purposes of this study, global adaptive behavioral development was quantified by the Vineland Adaptive Behaviors Scales, Interview Edition, Expanded Form, utilizing caretaker interview [Sparrow et al., 1984]. Adaptive Behavior Composite scores were derived from individual scores in three domains: Communication, Daily Living Skills, and Socialization.

Cognition. General intelligence and specific cognitive functions in 15 of the patients were assessed using a battery of neuropsychological test instruments. The 2 youngest patients (age 3 and 4 years) received intellectual assessment only. Table II lists the tests used and the cognitive functions which these tests are believed to measure. We assessed general intelligence, academic achievement, executive functions, attention, memory, visual-spatial skills, and motor function. Total time for testing was approximately 4–5 hr. To ensure comparability across tests, raw scores were rescaled to standard score equivalents (Z transformation) using the mean and standard deviation of age- and gender-matched healthy controls derived from published normative tables [Wechsler, 1945, 1967, 1974, 1981; Spreen and Gaddes, 1969; Gaddes and Crockett, 1975; Finlayson and Reitan, 1976; Power et al., 1979; Fromm-Auch and Yeudall, 1983; Dunn and Dunn, 1981; Curry et al., 1986; Beery, 1989; Halperin et al., 1989; Spreen and Strauss, 1991; Kirk, 1992; Saykin et al., 1994]. By definition, the control mean is represented by zero, with SD = 1 for all neuropsychological functions. A patient's score for each cognitive function was obtained by averaging the standard score equivalent of all tests measuring that function. In general, a score < -2 is considered impaired (Table II).

Maladaptive behavior. The Maladaptive Behavior Domain from the Vineland Scales was completed for all patients. In addition, both parents and a teacher completed the Steven Reiss Scales/Screen [Reiss, 1988, 1989] and the Thomas Achenbach Child Behavior Checklist (CBCL) [Achenbach, 1991] for 10 patients. Total scores from the Reiss Scales (used for patients <12 years old) and Reiss Screen (used for patients >12 years old), instruments developed for identifying mentally retarded persons who are likely to be in need of psychiatric services, were used because research indicates that only these scores are useful for the instruments' stated purpose [Aman, 1991]. The parent and teacher versions of the CBCL are commonly-used 113-item general screening behavioral checklists for identifying problematic behaviors in comparison to normal-IQ reference children and adolescents. Five patients, whose history or behavior was suggestive of possible autism, were assessed with the Autistic Diagnostic Interview-Revised (ADI-R) [Lord et al., 1994].

Structural brain imaging. Sixteen patients were evaluated with magnetic resonance imaging (MRI) at the University of Pennsylvania (using the same machine). MRI scans were analyzed by a radiologist who was blind to the clinical manifestations of all the patients.

Somatosensory-evoked potentials. Seven patients had somatosensory-evoked potentials determined. Results were analyzed independently by the electrodiagnostic laboratory in the Department of Neurology.

Chromosomal analysis. The methodology is described by Strathdee et al. [1995]. Briefly, chromosomes were G-banded using trypsin and Geimsa stain following standard protocols [Verma and Babu, 1989]. FISH was performed using lambda phage probes previously mapped to distinct regions on chromosome 18 by Southern hybridization to somatic cell hybrid panels [Kline et al., 1992, 1993]. In order to facilitate statistical analysis, breakpoints were plotted on an ideogram of the long arm of chromosome 18, and percentage deletion of the long arm was determined by physically

TABLE I. Summary of Demographic, Neurobehavioral, IQ, MRI, and SSEP Data*

Sex	Age (yr-mo)	Referral source	Neuropsychiatric history known at study accrual	Neuropsychiatric history emerging during study	Full scale IQ
M	4-4	Self-referred: speech delay	Speech problems	Peculiar attachment to inanimate object	65
M	10-0	Self-referred: behavioral problems	Aggressivity and temper tantrums	Severe temper tantrums; extreme stubborness	71
F	14-2	Self-referred: behavioral problems	Aggressivity and temper tantrums w/psych hosp	Severe temper tantrums; repeated knife attacks	65
M	14-11	Self-referred: behavioral problems	Odd mannerisms ("Is he autistic?")	Savant interest and memory for geography facts	48
M	16-5	Registry	Aggressivity and temper tantrums w/psych hosp	Severe temper tantrums; assaultive; school expulsion	71
M	16-10	Registry	Odd attachment to inanimate objects (autism?)	Explosive temper; in psychotherapy for 10 years	73
M	17-2	CHOP patient: behavioral problems	Aggressivity and temper tantrums w/psych hosp	Multiple psychiatric hosp; two school expulsions	55
M	22-7	18q− diagnosis	Aggressivity and temper tantrums	In intensive behavioral therapy	
F	29	CHOP patient	Conversion to ascetic religious sect	In psychotherapy for 10 years	
F	30	Registry	Aggressivity and severe assaultiveness	Repeated knife assaults; outpatient psychiatric tx	
F	32	From Donnai [1987]	Psych hosp for "mild OCD, panic attacks"	Psychiatric tx for about 10 years	
F	2-2	CHOP patient	None	No behavioral problems	
F	4-0	18q− diagnosis	None	No real problems per parents	61
F	5-6	18q− diagnosis	None	No behavioral problems	
M	7-9	CHOP patient	None	Autistic-like behavior but not referred to psychiatrist	
M	8-4	Registry	None	Impulsive, inappropriate, disruptive	60
M	8-9	18q− diagnosis	None	No behavioral problems	
M	9-1	18q− diagnosis	None	Parental neglect	
M	10-8	Registry	None	No beh problems per parents	<40
F	12-2	Registry	None	ADHD at age 7; on ritalin for 3 years; aggressive	
F	14-3	18q− diagnosis	None	No behavioral problems	
M	15-4	Registry	None	No behavioral problems	52
F	17-11	Registry	None	ADHD; on ritalin for about 10 years	51
F	18-6	18q- diagnosis	None	Inability to get along with family members	71
F	19-5	Registry	None	Referred to psychiatrist but has refused	
F	29-8	From Miller et al. [1990]	Slow, progressive onset of tx-refractory tremor at age 24	Psychiatric hosp for aggressivity and suicidality; molested as child	68
M	47-6	18q− diagnosis	Slow, progressive onset of tx-refractory tremor at age 30	Institutionalized for aggressivity and temper tantrums from age 22–27	57

measuring the portion of the long arm deleted for each patient.

RESULTS

Adaptive Behavior

Vineland Composite scores ranged from severely impaired to normal (23–97). The mean Vineland Composite score was statistically greater for females than for males (62 ± 5 vs. 43 ± 3; $t = 3.3$, $P = 0.004$). A repeated measures analysis of variance contrasting the three individual Vineland domains by sex revealed a statistically significant effect of sex ($F[3,24] = 6.3$, $P = 0.003$). For the group as a whole, males were significantly more impaired than females, with an effect size roughly equal to one SD. There was no difference in size of deletion between the sexes based on analysis of percentage deletion.

There was no significant correlation between deletion site and Vineland Composite or domain scores (Fig.

Vineland adaptive behavior composite	Vineland domains comm/ADL/ social	Vineland maladaptive domain	CBCL-18 mother father	TRF teacher's Achenbach	Reiss scales or screen	Autistic diagnostic interview (ADI-R)	MRI	SSEP
54	67/58/56	11/13	40/38/40 55/59/57		Negative	Negative	Normal	Normal
40	51/33/45	21/23	68/65/71 57/67/66	74/62/71	Positive	Positive	Abnormal	
83	85/99/78	18/26			Positive		Abnormal	
63	85/40/80	11/14	48/43/53 51/43/58	46/39/52	Negative	Positive	Abnormal	Normal
48	47/60/46	14/17			Positive		Normal	
42	55/36/46	13/16			Positive	Positive	Abnormal	
41	38/40/56	14/19					Abnormal	
31	21/39/41	13/16						
97	97/103/96	5/5					Abnormal	
59	81/58/55	14/15			Positive			
67	77/73/73							
59	71/64/67	4/4	34/30/34 46/30/40	53/57/58	Positive			
73	73/69/76	7/7						
32	35/<20/49	18/21				Positive	Abnormal	
51	51/43/71	5/5	43/44/45 46/46/51	67/65/73	Positive		Normal	Abnormal
23	24/<20/34	10/15						
39	40/37/51	3/5						
37	40/31/48	16/16	55/49/55 55/49/56	53/58/57	Positive			
49	62/47/52	17/18	49/54/62	60/59/65	Positive		Abnormal	Abnormal
76	88/81/76	5/5						
58	55/65/71	3/3	39/43/45 32/32/28	51/55/51	Negative		Normal	Abnormal
25	26/25/33	10/11	52/51/57 58/49/60	58/63/57	Negative (on ritalin)		Abnormal	Normal
51	53/52/60	17/17	64/56/66 59/57/64	66/59/66	Negative		Abnormal	
48	41/66/49	23/28						
62	51/90/62	16/20					Abnormal	Abnormal
39	24/57/69	22/28			Positive		Abnormal	

*CHOP, Children's Hospital of Philadelphia; hosp, hospitalization; OCD, obsessive-compulsive disorder; tx, treatment; beh, behavioral; ADHD, attention deficit hyperactivity disorder; ADL, activities of daily living.

1). Nor was there significant correlation between these measures and age.

Cognition

Overall, full-scale IQ (FSIQ) scores ranged from borderline to severely impaired (FSIQ = 73–<40; mean FSIQ = 61 ± 10; VIQ = 64 ± 9; PIQ = 61 ± 11). Consistent mild-to-moderate deficits were found across all IQ subtests. There was no significant correlation between deletion size and full-scale IQ scores for either males or females. On average, academic achievement in reading, spelling, and arithmetic was commensurate with IQ (Fig. 2), though one patient did have achievement scores significantly below his IQ. However, there was no statistically significant correlation between IQ and achievement scores on a case-by-case basis. Comparison of patients' scores to published norms on tests in the neuropsychological assessment battery measuring specific cognitive functions indicated performance two or more SD below the mean in all functional area (Fig. 3).

TABLE II. Neuropsychological Battery With Tests Grouped by Function (Functions Which Tests Are Thought to Measure)

Intellectual (global intelligence):
Wechsler Adult Intelligence Scale-Revised (WAIS-R)
Wechsler Intelligence Scale for Children-Revised (WISC-R)
Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
Achievement (academic achievement in reading, spelling, arithmetic):
Wide Range Achievement Test-Revised
Executive function (problem solving, planning, cognitive flexibility):
Weigl Color Form Sorting Test
Trail Making Test B (Halstead Reitan Battery)
Attention (attention, vigilance, freedom from distractibility):
Gordon Diagnostic Systems Continuous Performance Test
Verbal memory (immediate and delayed free recall):
Wechsler Memory Scale—Logical Memory Passages I and II
Visual Memory (immediate and delayed free recall):
Wechsler Memory Scale—Visual Reproduction I and II
Language (naming, verbal fluency, receptive vocabulary):
Boston Naming Test (visual confrontation naming)
Controlled Oral Word Association Test (word list generation to phonemic cue/verbal fluency)
Animal Naming (word list generation to semantic cue/verbal fluency)
Peabody Picture Vocabulary Test-Revised (receptive vocabulary)
Visual-Spatial (visuospatial motor integration):
Beery Developmental Test of Visual Motor Integration
Motor (fine motor speed and dexterity):
Finger Oscillation Test (Halstead Reitan Battery)

There was no significant effect of gender on intellectual performance ($F[3,9] = 1.451$, $P = 0.292$), achievement ($F[3,8] = 2.279$, $P = 0.156$), or neuropsychological functioning ($F[6,3] = 3.114$, $P = 0.190$) in the subset of patients tested. There was no significant correlation between level of cognitive impairment and age. There were no statistically significant correlations between deletion size and general intelligence, achievement, or specific neuropsychological performance. Furthermore, there was no significant effect of deletion size when deletions were transformed into a dichotomous variable, i.e., largest third vs. smallest third (≥30% deletion vs. ≤21% deletion).

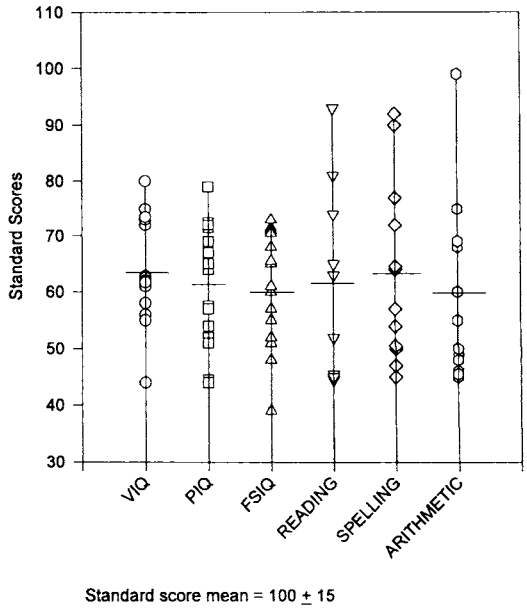

Fig. 2. Age-corrected standard scores, IQ and achievement. Full-scale, verbal, and perceptual-organizational (nonverbal) intelligence, and single-word reading, spelling, and arithmetic achievement by patient compared to age-matched normals. Normal mean score is 100 ± 15.

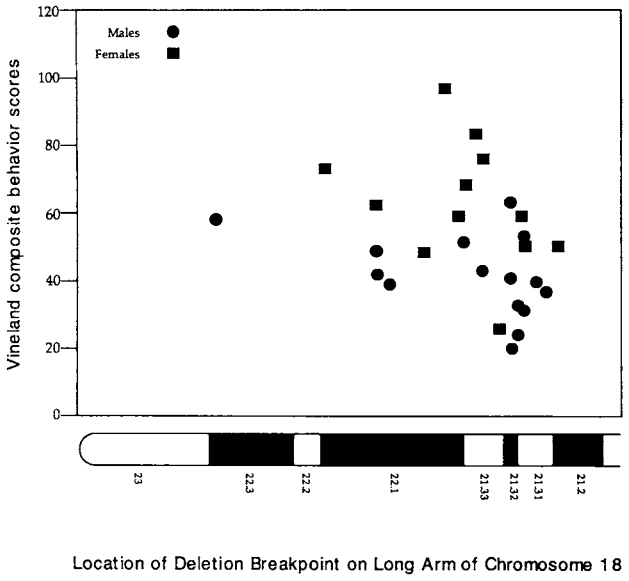

Fig. 1. Vineland composite behavior scores and deletion breakpoint. Normal Vineland adaptive behavior composite score mean is 100 ± 15. Less than 70 is considered impaired.

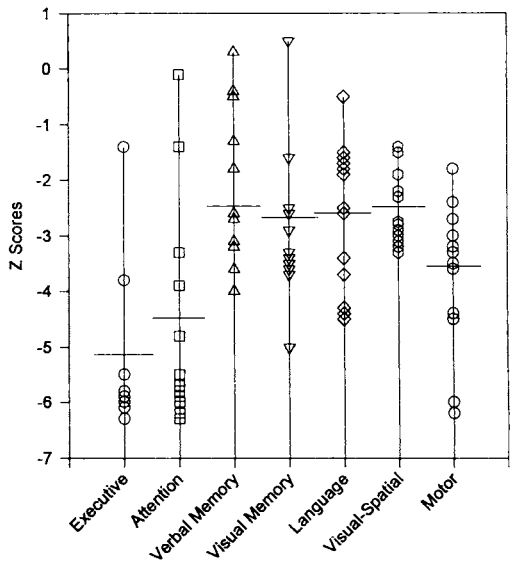

Fig. 3. Performance by neuropsychological function, z-transformed.

Maladaptive Behavior

In the total sample of 27 patients, there were 14 patients older than age 5 years whose behavioral histories were not known at accrual for this study. These patients were all Caucasian, from Hollingshead social classes I–IV, residing in different regions of the U.S. Eight (57%) had Vineland Maladaptive Behavior Domain scores that were *significant*, 3 (21%) that were *intermediate*, and 3 (21%) that were *nonsignificant*.

Among the 8 postpubescent patients, 6 (75%) had scores that were *significant*. Excluding 1 patient already being treated with Ritalin, 71% of patients had positive scores on the Reiss Scale or Screen, i.e., they were likely to be in need of psychiatric services. On the Achenbach scales, 2 of these 7 postpubescent patients (29%) had T scores in the clinically significant range on the parent version; 3 (43%) had clinically significant scores on the teacher version. Interestingly, among 9 patients for whom both parent and teacher Achenbach ratings were available, 7 (78%) were given greater maladaptive scores by the teacher than by the parents.

The ADI-R was administered to the parents of 5 patients whose history was suggestive of an autistic-like syndrome. However, of the 16 patients whose behavioral histories were completely unknown prior to this study, only 1 was suspected of autism based on later related history, and scored positive on the ADI-R. Thus, our initial estimate of the prevalence of autism in 18q- syndrome is 6% (1 of 16), probably no higher than any other syndrome with a comparable degree of cognitive disability [Einfeld and Hall, 1992].

Structural Brain Imaging

Thirteen of 16 patients (81%) had abnormal MRI findings, most notably patchy white-matter hyperintensities on T2-weighted images, similar to those first described by Miller et al. [1990]. There was no obvious relationship between deletion size and MRI abnormalities (see Loevner et al., in preparation, for more detail).

Somatosensory-Evoked Potentials

Four of 7 patients had abnormal somatosensory-evoked potentials (SSEPs). All of the abnormalities consisted of slowed central conduction velocities, similar to those described by Miller et al. [1990] in a single patient. Of note, the patient with the smallest chromosomal deletion and the patient with the largest chromosomal deletion had abnormal SSEPs, while some of the patients with intermediate deletions had normal SSEPs (Table I). No patients had evidence of slowed peripheral conduction velocities.

DISCUSSION

The present investigation involved the largest series of 18q- patients ever reported in one study. Our most important finding was the complete absence of any obvious relationship between chromosomal deletion size and every one of our neuropsychiatric measures. The only variable that had any value for predicting developmental outcome in these patients was gender: females had Vineland Composite scores one full SD higher than males, roughly the difference between a diagnosis of mild and moderate mental retardation.

General intelligence of the current sample of 18q- patients was generally within the range that has previously been reported in the literature, from borderline (FSIQ $\leq$73) to severely impaired (FSIQ $<$40). Results of neuropsychological testing revealed no specific pattern of cognitive strengths or weaknesses and were not generally supportive of focal deficits involving, for instance, language. Rather, cognition was broadly impaired with moderate-to-severe deficits evident across all functional domains, including attention, verbal and visual memory, language, motor skills, visual-spatial ability, and executive skills. The single group of tasks that may have been preferentially impaired were those thought to be mediated by the frontal lobes, i.e., problem solving, cognitive flexibility, and motor control, as assessed by the Weigl Color Form Sorting Test and the Halstead Reitan Trail Making Test B (Fig. 3).

A recurrent concern of parents, teachers, and physicians during this study was the possibility of long-term cognitive decline. For the oldest patient in this study (age 47), Wechsler Adult Intelligence Scale (WAIS) IQ data were available from a long-term care admission at age 22; these scores demonstrated that there had been no change during the intervening decades, despite the development of a progressive and debilitating tremor similar to that described by Miller et al. [1990]. Three other patients (ages 14, 16, and 17) with prior Wechsler Intelligence Scales for Children-Revised (WISC-R) scores also showed no meaningful changes over time. Thus, while patients with 18q- may be at increased risk for development of an idiopathic tremor in adulthood [Miller et al., 1990], we found no evidence for clinically significant long-term changes in general intelligence.

Most of the patients in this study had had previous contact with the mental health system, with impulsivity, aggressivity, and temper outbursts the most commonly reported behavior problems (Table I). To limit possible bias towards accrual of patients with neuropsychiatric problems, we were particularly concerned to identify patients whose behavioral histories were completely unknown to us. The data summarized in Table I indicate that most of these patients also have at least mild behavioral problems. This was particularly true for postpubescent patients. We conclude that behavioral problems are common in persons with 18q- syndrome, and since they appear to be persistent, such problems probably should be addressed as early as possible. Our data are consistent with those of others [e.g., Seshadri et al., 1992] who have observed autistic behaviors in children with 18q- syndrome, but we were unable to confirm the reports of those who have reported psychosis, present or past, or any other neuropsychiatric disorders such as depression, mania, obsessions, compulsions, panic, tics, etc.

The present findings are consistent with those of Miller et al. [1990], who first described MRI and SSEP abnormalities in a patient with 18q-. Loevner et al. (in preparation) will describe the MRI findings in detail, but we think it notable that there was considerable variability in the range of brain regions affected by the white-matter hyperintensities on T2-weighted images. We also think it worthwhile to reemphasize that the patients with the largest and smallest deletions, dele-

tions differing by roughly 19 million base pairs, both had abnormal SSEPs, while patients with intermediate deletions either did or did not have abnormal SSEPs. This observation is similar to our observation of the lack of relationship between 18q deletion size and the presence or absence of selective IgA insufficiency [Strathdee et al., 1995], and again points out the lack of any 1-to-1 correlation between deletion size and clinical phenotype.

In conclusion, the present findings represent a first attempt to systematically characterize quantitative relationships between deletion size and neuropsychiatric phenotype in 18q− syndrome. Since our data are not consistent with hypotheses of single-gene defects causing any of the neuropsychiatric phenomena seen in this syndrome, future studies with much larger sample sizes will be needed in order to test multigene hypotheses. Probably the most useful next step in the effort to generate hypotheses involving other genes would involve neuropathological studies of patients with various 18q deletions. Unfortunately, many barriers prevent the successful implementation of such studies.

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